

Application No.: 09/900,766

Docket No.: HO-P02188US0

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Goran Forsberg et al.

Application No.: 09/900,766

Confirmation No.: 7699

Filed: July 6, 2001

Art Unit: 1645

For: NOVEL ENGINEERED SUPERANTIGEN FOR
HUMAN THERAPY

Examiner: P. A. Duffy

DECLARATION UNDER 37 CFR §1.132

Dear Sir:

I, Göran Forsberg, Ph.D., do hereby declare as follows:

1. I am a citizen of Sweden, residing at Sturegatan 52, 241 31 Eslöv Sweden.
2. I am employee of the assignee of the above-referenced patent application ("Application"), I am a coinventor of the Application, and I am familiar with the contents of the Application.
3. Currently, I am Head of the Department of Scientific Affairs at Active Biotech AB. I am skilled in the areas of molecular and cell biology, immunology, biochemistry and cancer therapies.
4. I am very familiar with the 5T4 antigen and have been responsible for studies (including studies where I have been a co-author) on the expression of 5T4 in normal and malignant tissues.
5. The 5T4 antigen is an oncofetal protein normally found on human trophoblasts. 5T4 is also expressed on a variety of different solid tumors. These include Non-small cell lung cancer, Renal cell cancer, Pancreatic cancer, Breast Cancer, Colon cancer,

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Ovarian cancer, Stomach cancer, Cervix cancer as well as Prostate cancer (Table 1). A weak reactivity has occasionally been found on certain normal tissues as described by Forsberg et al., 2001 (Table 2). In general, this type of normal tissue reactivity is very limited as compared to most known cancer antigens. Examples of staining of cancer tissue and normal tissue are shown in Figure 1.

Table 1. 5T4 reactivity in a variety of tumor types.

Cancer	Stage	Reactivity	Reference	Comments
NSCLC	Mixed	10/10 7/7	Southall 1990 Forsberg 2001	Most or all patients express 5T4 antigen.
Breast	Mixed	5/5 6/6	Southall 1990 Forsberg 2001	Most or all patients express 5T4 antigen
Renal	Clear Cell	1/1 20/20	Southall 1990 unpublished	Most or all clear cell tumors (the most common form of kidney cancer) express 5T4.
Pancreatic	Mixed	3/3 20/20	Southall 1990 unpublished	More than 95% of tumors express 5T4.
Ovarian	Mixed	4/7	Southall 1990	More than 70% of ovarian cancers are 5T4 positive.
	I	2/10	Wrigley 1995	For stage IV patients, 90-95% of the patients are 5T4 positive
	II	4/57	Wrigley 1995	
	III	21/29	Wrigley 1995	
	IV	24/26	Wrigley 1995	
Colorectal	Mixed	4/13	Southall 1990	40-50% of colorectal cancers express 5T4. In Dukes stage D patients, more than 70% overexpress the antigen.
	A	2/8	Starszynska 1992	
	B	7/34	Starszynska 1992	
	C	13/21	Starszynska 1992	
	D	7/9	Starszynska 1992	
Gastric	Mixed	6/7 35/86	Southall 1990 Starszynska 1998	Approximately 50% of gastric cancers have 5T4 positive cells. Most samples with 5T4 negative cells have 5T4 positive tumor stroma (Starszynska 1998) making more than 95% of the tumors 5T4 positive.
	I	1/2	Starszynska 1992	
	II	1/4	Starszynska 1992	
	III	1/1	Starszynska 1992	
	IV	12/20	Starszynska 1992	
Prostate	Mixed	2/2	unpublished	
Cervix	Mixed	5/5	Southall 1990	Between 85 and 90% of patients express 5T4 antigen.
	I	22/25	Connor 1990	
	II	22/26	Connor 1990	
	III	9/10	Connor 1990	
	IV	5/6	Connor 1990	

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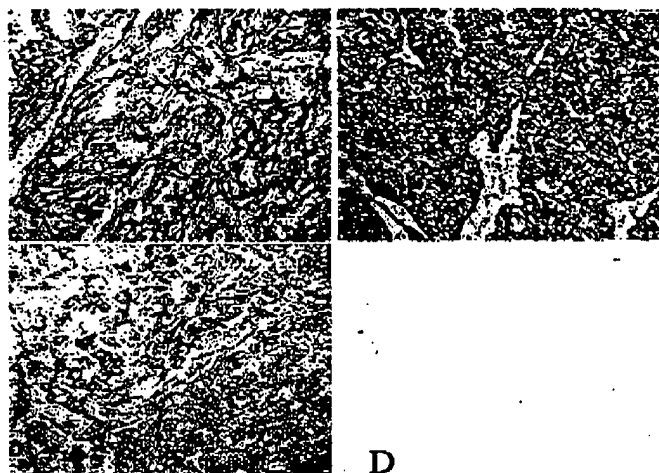
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Table 2 5T4 Normal tissue reactivity

Tissue	Reactivity	Comment
CNS (n=1)	neg.	
Skin (n=2)	neg.	
Myocardium (n=4)	+	Reaction in the luminal outline of a subpopulation of muscular vessels in 2/4 samples.
Adrenal (n=2)	neg.	
Kidney (n=4)	+ - ++	Diffuse reaction in glomeruli and parietal layer outlining Bowman's capsule (2/4). Weak focal reaction outlining lumen in occasional muscular vessels (2/4).
Lung (n=4)	+ - ++	Weak luminal outline in occasional vessels (2/4). Moderate reaction in a basal epithelial cellular or matrix component associated with the bronchial epithelium
Liver (n=4)	+	Occasional staining of the sinusoidal outline close to the central vein (1/4).
Pancreas (n=2)	+ - ++	Weak-moderate reaction in occasional pancreatic ducts and scarce stromal structures. Weak focal reaction outlining lumen in occasional muscular vessels.
Gastro-intestinal tract (stomach n=2, small intestine n=2 and large intestine n=4)	++	Reaction in some cell type or extracellular component of the epithelial basal lamina or the lamina propria in parts of the surface epithelium.
Pharynx (n=2)	+ - ++	Reaction in squamous epithelium (most prominent in basal layer).
Thyroid (n=2)	+	Reaction associated with follicular epithelial cells. Focal reaction outlining lumen of occasional muscular vessels.
Spleen (n=2)	+	Focal reaction outlining lumen of occasional muscular vessels.

Figure 1. 5T4 reactivity on NSCLC (A), renal cell carcinoma (B) and pancreatic cancer (C). The tumors are stained with a streptavidin-peroxidase technique giving a brown reaction product. For comparison a negative control is shown in D.



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6. I hereby declare that all statements made herein on my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: Sept 1, 2005
Göran Forsberg, Ph.D.